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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/942,024	08/28/2001	Lance E. Steward	17452 (BOT)	7269

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/942,024	STEWARD ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-100* is/are pending in the application.

4a) Of the above claim(s) *37,62 and 84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,36,38-61,63-83 and 85-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

The amendment filed 2-22-05 has been entered into the record. Claims 1-31 have been cancelled. Claims 35-100 are pending. Claims 35, 36 and 38-61, 63-83 and 85-100 are under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Election/Restrictions

This application contains claims 37, 62, 84 are drawn to an invention nonelected with traverse in the Response filed 7-28-03. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections Withdrawn

The rejection of claims 35, 36 and 38-53 under 35 USC 103(a) is withdrawn in view of the amendments to the claims.

The rejection of claims 35, 36 and 38-47 under 35 USC 102(e) as being anticipated by Schmidt et al U.S. Patent No 6,762,280 is withdrawn in view of the amendments to these claims.

Rejections Maintained

The provisional rejection of claims 25, 36, 38, 39, 41, 42, 44, 45, 47, 48 and 53 as unpatentable over claims 61-63, 67, 71-74 of US Application Serial number 10/261,161 is maintained for reasons made of record.

Applicants did not traverse this rejection. Applicants indicate deferral of a response until allowable subject matter has been indicated. This is not persuasive.

Allowable subject matter will not be indicated until such time as Applicants obviate this provisional rejection.

New Rejections Based on Amendment

Claims 68-72 and 90-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

All claims are confusing for the following reasons. The base claim requires a donor fluorophore and an acceptor whose adsorption and emission spectrum is not defined. The acceptor does not even have to be a fluorophore. Therefore, it is unclear how one measures the resonance energy transfer to an acceptor that is not clearly defined in the claims. What is the acceptor and how is it measured ? The acceptor is not defined as a fluorophore, but merely having an absorbance spectrum. An acceptor that adsorbs does not have to emit (i.e. the acceptor could quench). Each of the claims are confusing because they lack clear antecedent basis in the previous claims because the acceptor is not particularly defined and the steps lack clear antecedent basis in the independent claim. Additionally, the independent claims requires determining a difference resonance energy transfer relative to a control substrate, yet the dependent claims recite specific parameters that are not particularly required by either the donor or acceptor of the assay and it is unclear under what conditions a difference is seen and what the difference is. FRET energy transfer is determined by measuring acceptor fluorescence. Further, the claim does not define appropriate conditions (i.e. non-cleaved or cleaved), as such it is not clear if the pair quenches initially or exhibits resonance energy transfer initially. The conditions under which resonance energy transfer is exhibited are not defined by the claim and it is not clear that the acceptor is fluoresces or quenches the donor upon energy transfer.

Claims 35, 36 and 38-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As to claims 35, 36 and 38-59, the specification at page 40 does not provide written description for generic BoNT/A substrate of 69 or 72 amino acids long. The passage only supports *recognition sequences* from a specific residue range of human SNAP-25. The passage does not contemplate the specific number of amino acids in a as filed does not provide written description support for the now recited 69 or 72 amino acids in general as it relates to any generic sequence. Additionally, the range of residues specifically recited provides for a specific sequence of human SNAP-25 that is 70 or 73 amino acids in length. Further, this passage does not provide *substrate* lengths of 19, 20, 21, or 22 amino acids long. The concept of substrate lengths is different as compared to recognition sequences as set forth in the claims and as defined in the specification. Therefore, teachings of lengths of "recognition sequences" drawn to a particular sequence cannot support the same for the now recited "substrate". The passage does not support the particular substrates inasmuch as the recognition sequences set forth therein are 13, 15, 16, 17, 18, 70 and 73 amino acids long. There is no generic conception of the now claimed discrete lengths in any recognition sequence in this passage. Applicants also specifically point to page 115 of the specification for teachings for the now recited limitations. This is not persuasive, while the specification teaches specific FRET substrates having specific sequences and specific donors and acceptors attached thereto, the species described on page 115, do not provide conception of a genus of substrates with the absolute lengths of 19, 20, 21, 22, 69 and 72 amino acids as now claimed. To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the

invention and that the invention, in that context, is whatever is now claimed. See MPEP 2163.02. Also, the failure to meet the written description requirement under 35 USC 112, first paragraph arises when the claims are changed after the filing date to change the scope of the disclosure, which does encompass setting forth subgeneric claims (see MPEP 2163.05). In the instant case the specification contemplates generic substrates and exemplifies specific sequences at page 115. The specific sequences in combination with the length limitations provide for a new subgenus comprising a substrate of undefined structure but absolutely defined length. The specification as filed does not provide for conception by way of written description for this new subgenus.

As to the embodiments providing for FRET using peptides of 69 and 72 amino acids long. The specification as filed fails to describe any FRET pair that provides energy transfer across ranges across peptides at this great distance. As such, Applicants could not have been in possession of the claimed invention.

Claims 60, 61 and 63-68 and 74-78 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Schmidt et al (US Patent No. 6,762,280, with priority to the BoNT/A peptide FRET substrate assay for detection of BoNT/A as cited in the provisional 60/235,050 filed September 20, 2000).

Applicants have reintroduced the previous version of claim 35 as new claim 79. Therefore, this claim stands rejected over the substrate of SEQ ID NO:1 in the BoNT/A FRET assay as disclosed in the provisional document. Applicants argue that the peptide of SEQ ID NO:1 does not have at least six consecutive residues of human SNAP-25 (SEQ ID NO:2) comprising Gln197-Arg198 and as such claims 60-78 avoid the previously cited prior art. This is not persuasive, the claims recite "or a peptidomimetic thereof". Peptidomimetics as set forth at page 37-38 is a peptide-like molecule that is cleaved by the same clostridial toxin upon which it is based. It is noted that the peptide of Schmidt et al is based on the human SNAP-25 sequence since they share 5 consecutive amino acids

in common (see Response, page 19, Table 1). Applicants' arguments are not commensurate in scope with the claims and as such not persuasive, in view of the language of "peptidomimetic" of this claim. Applicants are reminded, that where the reference U.S. patent or U.S. patent application publication claims the same patentable invention a declaration pursuant to 37 CFR 1.131 cannot obviate the reference.

Claims 69, 70 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al (US Patent No. 6,762,280, with priority to the BoNT/A peptide FRET substrate assay for detection of BoNT/A as cited in the provisional 60/235,050 filed September 20, 2000) in view of Clegg et al (Current Opinion in Biotechnology 6:103-110, 1995).

Schmidt et al is set forth supra. Schmidt et al differ by not measuring donor fluorescence or measuring at multiple times.

Clegg et al teach that FRET assays with doubly labeled molecules are especially useful for continuously following or detecting activity of proteases or peptidases (i.e. the multiple independent measurements over time). Clegg et al also teach sensitive FRET measurements on cells can be made by analyzing the polarization of the donor and/or acceptor emission.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to modify the assay of Schmidt by measuring the donor emission as a means to detect FRET continuously at multiple time points because Clegg et al teach that Fret assays with doubly labeled molecules are useful for continuously following activity of proteases and sensitive FRET measurements on cells can be made by analyzing the polarization of the donor or acceptor emission. Further, it would be *prima facie* obvious to measure both donor and acceptor emission to ensure confidence of the assay by comparing both independent measures of FRET.

Claim 72 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al (US Patent No. 6,762,280, with priority to the Bunt/A peptide FRET substrate assay for detection of Bunt/A as cited in the provisional 60/235,050 filed September 20, 2000) in view of Siegel et al (STKE, June 27, 2000 of record)

Schmidt et al is set forth supra. Schmidt et al differ by not measuring the excited state lifetime of the donor fluorophore as a means to detect FRET.

Siegel et al teach that FRET also manifests itself as decreases in the donor's excited state lifetime and fluorescence intensity. Siegel et al also teach that measurements of the donor lifetime are an elegant way to measure FRET (page 4, column 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to modify the assay of Schmidt by measuring the donor excited state lifetime as a means to detect FRET because Siegel et al teach that measurements of the donor lifetime is an elegant way to measure FRET.

Claim 71 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al (US Patent No. 6,762,280, with priority to the BoNT/A peptide FRET substrate assay for detection of BoNT/A as cited in the provisional 60/235,050 filed September 20, 2000) in view of Auwerx et al (US 2003/0104975, published June 5, 2005 with priority to 60/297,772 filed June 14, 2001).

Schmidt et al is set forth supra. Schmidt et al differ by not measuring the emission maximum shift or ratio of fluorescence amplitudes (i.e. intensities).

Auwerx et al teach at [0279] and pages 8-9 of the provisional that FRET can be manifested as a reduction in the intensity of the fluorescence emission from the donor moiety, reduction in the lifetime of the excited state of the donor moiety, or emission of fluorescent light at the longer wavelengths (lower energies) characteristic of the acceptor moiety when the sample is excited at a wavelength that is optimal for the donor. Intensity

of the fluorescent signal from the donor, intensity of the fluorescent signal from the acceptor, the ratio of the fluorescence amplitudes near the donor's emission maximum, or the excited state lifetime of the donor can be monitored. Changes in the amount of FRET can be determined as a change in the ration of the amount of fluorescence from the donor and acceptor moieties. Changes in the absolute amount of indicator, changes in the excitation intensity, and changes in the turbidity or other background absorbances n the sample and at the excitation wavelength affect the intensities of fluorescence from both the donor and acceptor are approximately in parallel. Therefore the ratio of the two emission intensities is a more robust and preferred measure of cleavage than either intensity alone. Protein fusions containing BFP and GFP linked together have been employed for example in protease assays.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to modify the assay of Schmidt et al as set forth supra by measuring any of the donor and/or acceptor parameters as set forth by Auwerx et al as a means to detect FRET because Auwerx et al teach conventional means of measuring FRET and indicate that the ratio of the two emission intensities is a more robust and preferred measure of cleavage than either intensity alone.

Claim 60, 61, 63-70, 73-78, 79-83, 85-92, 95-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al (US Patent No: 5,965,699 issued October 12, 1999) in view of Mahajan et al (Chemistry and Biology, 6:401-409, 1999) and Clegg et al (Current Opinion in Biotechnology 6:103-110, 1995).

- Schmidt et al teach multiple peptides having at least 6 consecutive residues of human SNAP-25 (SEQ ID NO:2) said six consecutive residues comprising Gln197-Arg198. In particular, Schmidt et al teach multiple peptides (see SEQ ID NO:1 and columns 4-5). Each of the peptides is suitable substrate for assaying the proteolytic activity of serotype A from Clostridium botulinum (i.e. the instant BoNT/A) in a fluorescent assay.

Schmidt et al teach the assay using the substrates and that the assay is useful for determination of neurotoxin A enzymatic activity in drugs, solutions or samples (column 2). Samples include, food, soil, beverages, lotions, clinical drugs and solutions (column 3, third full paragraph). Schmidt et al differ in not performing a FRET assay using genetically encoded fuorophores or acceptors.

Mahajan et al teach an in vitro FRET assay for capases. Capases are specific enzymes involved in apoptosis. The capase substrate was a recombinant fusion protein comprising mutant green fluorescent protein substrates, where the enzyme recognition sequence was inserted between cyan fluorescent protein and yellow fluorescent protein. Purified substrates were cleaved following exposure to purified enzymes (page 403, column 2 - page 404, column 1).

Clegg et al teach that FRET assays with doubly labeled molecules are especially useful for continuously following or detecting activity of proteases or peptidases (i.e. the multiple independent measurements over time). Clegg et al also teach sensitive FRET measurements on cells can be made by analyzing the polarization of the donor and/or acceptor emission. Clegg et al teach that FRET provides for high sensitivity, specificity, non-invasiveness, rapidity and relative simplicity.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to substitute the BoNT/A substrate for the capase substrate in the FRET fusion protein and use the modified fusion protein to detect BoNT/A activity in vitro as an alternative to the fluorescent assay of Schmidt et al because the assay as combined would reduce the number of assay steps by omitting the independent addition of fluorescamine and provide the advantage for continuously following neurotoxin protease activity and monitoring the protease activity over time. Further, it would have been obvious to one having ordinary skill in the art at the time that the invention was made that the assay as combined would have the benefit of substantially

obviating background levels in food and other samples containing endogenous free amino groups that would otherwise bind the fluorescamine.

Claims 72 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al (US Patent No: 5,965,699 issued October 12, 1999), Mahajan et al (Chemistry and Biology, 6:401-409, 1999) and Clegg et al (Current Opinion in Biotechnology 6:103-110, 1995) as applied to claims 60, 61, 63-70, 73-78, 79-83, 85-92, 95-100 above and further in view of Siegel et al (STKE, June 27, 2000 of record).

The combination of Schmidt et al (US Patent No: 5,965,699 issued October 12, 1999) , Mahajan et al (Chemistry and Biology, 6:401-409, 1999) and Clegg et al (Current Opinion in Biotechnology 6:103-110, 1995) is set forth supra. The method as combined differs by not measuring not measuring the excited state lifetime of the donor fluorophore as a means to detect FRET.

Siegel et al teach that FRET also manifests itself as decreases in the donor's excited state lifetime and fluorescence intensity. Siegel et al also teach that measurements of the donor lifetime are an elegant way to measure FRET (page 4, column 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to modify the assay as combined supra by measuring the donor excited state lifetime as a means to detect FRET because Siegel et al teach that measurements of the donor lifetime is an elegant way to measure FRET.

Claims 71 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al (US Patent No: 5,965,699 issued October 12, 1999), Mahajan et al (Chemistry and Biology, 6:401-409, 1999) and Clegg et al (Current Opinion in Biotechnology 6:103-110, 1995) as applied to claims 60, 61, 63-70, 73-78, 79-83, 85-92, 95-100 above

and further in view Auwerx et al (US 2003/0104975, published June 5, 2005 with priority to 60/297,772 filed June 14, 2001).

The combination of Schmidt et al (US Patent No: 5,965,699 issued October 12, 1999) , Mahajan et al (Chemistry and Biology, 6:401-409, 1999) and Clegg et al (Current Opinion in Biotechnology 6:103-110, 1995) is set forth supra. The method as combined differs by not measuring the emission maximum shift or ratio of fluorescence amplitudes (i.e. intensities).

Auwerx et al teach at [0279] and pages 8-9 of the provisional that FRET can be manifested as a reduction in the intensity of the fluorescence emission from the donor moiety, reduction in the lifetime of the excited state of the donor moiety, or emission of fluorescent light at the longer wavelengths (lower energies) characteristic of the acceptor moiety when the sample is excited at a wavelength that is optimal for the donor. Intensity of the fluorescent signal from the donor, intensity of the fluorescent signal from the acceptor, the ratio of the fluorescence amplitudes near the donor's emission maximum, or the excited state lifetime of the donor can be monitored. Changes in the amount of FRET can be determined as a change in the ration of the amount of fluorescence from the donor and acceptor moieties. Changes in the absolute amount of indicator, changes in the excitation intensity, and changes in the turbidity or other background absorbances n the sample and at the excitation wavelength affect the intensities of fluorescence from both the donor and acceptor are approximately in parallel. Therefore the ratio of the two emission intensities is a more robust and preferred measure of cleavage than either intensity alone. Protein fusions containing BFP and GFP linked together have been employed for example in protease assays.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to modify the assay of Schmidt et al as set forth supra by measuring any of the donor and/or acceptor parameters as set forth by Auwerx et al as a means to detect FRET because Auwerx et al teach conventional means of measuring

FRET and indicate that the ratio of the two emission intensities is a more robust and preferred measure of cleavage than either intensity alone.

Status of Claims

Claims 35, 36 and 38-61, 63-83 and 85-100 stand rejected. Claims 37, 62 and 84 have been withdrawn from consideration.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy

Primary Examiner

Art Unit 1645